

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

Rec'd PCT/

20 DEC 2004
116855
WIPO
COMPLIANCE

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C08G 18/10, 18/32, A61L 27/00	A1	(11) International Publication Number: WO 97/22643 (43) International Publication Date: 26 June 1997 (26.06.97)
(21) International Application Number: PCT/SE96/01530		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 25 November 1996 (25.11.96)		
(30) Priority Data: 9504495-4 15 December 1995 (15.12.95) SE		
(71) Applicant (for all designated States except US): POLYRAND AB [SE/SE]; Ryetvägen 5, S-436 55 Hovås (SE).		
(72) Inventor; and		Published
(75) Inventor/Applicant (for US only): FLODIN, Per [SE/SE]; Ryetvägen 5, S-436 55 Hovås (SE).		<i>With international search report. In English translation (filed in Swedish).</i>
(74) Agents: GRAUDUMS, Valdis et al.; Albihn West AB, P.O. Box 142, S-401 22 Göteborg (SE).		
(54) Title: LINEAR BLOCK POLYMER COMPRISING UREA AND URETHANE GROUPS, METHOD FOR THE PRODUCTION OF LINEAR BLOCK POLYMERS AND USE OF THE BLOCK POLYMERS AS IMPLANTS		
(57) Abstract		
<p>The present invention relates to a linear block polymer which is particularly suitable for use as an implant in humans or animals, for example as ligaments. The block polymer comprises urea and urethane groups and has a molecular weight of at least 10^4 Dalton, preferably at least 10^5 Dalton and it also includes primary NH₂ and/or OH end groups. Besides the use of the block polymer as an implant in a biological environment, the invention also includes a method for the production thereof, which method is characterized in that a prepolymer having two isocyanate end groups per molecule is chain extended with an aliphatic or aromatic diamine with a mol ratio NH₂/NCO of 0.95 to 1.05.</p>		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

5 TITLE: Linear block polymer comprising urea and urethane groups, method for the production of linear block polymers and use of the block polymers as implants.

FIELD OF THE INVENTION:

10 The present invention relates to a linear block polymer which comprises urea and urethane groups and which has a high molecular weight and which is suited as an implant in living beings such as humans and animals. The invention also comprises a method for the production of the block 15 polymer in question and use thereof as an implant, for example, an implant in the form of ligaments.

PRIOR ART:

20 When injuries arise on the body of a human or an animal or as a result of some disease, a damaged organ must often be replaced temporarily or permanently by some kind of implant. A condition for such an implant to be able to be used is that, firstly, it has such properties, for example strength, that it can replace the functions of the damaged 25 organ and, secondly, that it is biocompatible, i.e. that the body is not poisoned or in some other way damaged by the implant. Different materials, such as pure titanium and some kinds of plastic materials have been shown to have these properties and are already used to a great extent. 30 Other materials are also known in this connection.

35 The metallic implants, such as titanium and some types of steel are characterized by their great strength and they are therefore used, for example, as tooth implants or for repairing bone fractures, etc. Surgically inserted reservoir containers for medicines which are to be dosed in small amounts during an extended period of time are preferably made of titanium. Different forms of pipes which can replace blood veins or drain out some body liquid are

used and these are usually made of thermoplastic materials. They may be used both temporarily and permanently.

TECHNICAL PROBLEM:

5 Some implants, such as implants for replacing or supporting a ligament, must have a certain tension strength and have an adapted stretchability. In addition, it is necessary for such an implant that it is also biocompatible and it is also desirable that the implant can promote the growth of
10 the damaged natural ligament at the same time as the implant in many cases should be biologically degradable so that it slowly disappears and the rebuilt ligament resumes its function again.

15 **SOLUTION:**

According to the present invention, the above problems have been solved and an implant has been created using a new linear block polymer having a molecular weight of at least 10⁴ Dalton, preferably at least 10⁵ Dalton, comprising urea and urethane groups and comprising primary NH₂ and/or OH end groups.
20

According to the invention, the linear block polymer should have at least as many or more urea groups as urethane groups.
25

The linear block polymer according to the present invention can, in the chain, also contain such groups as polytetramethylene oxide, polyethylene oxide, polycaprolactone, polyethylene glycol adipate, toluylene, diphenyl methane, hexamethylene, tetramethylene, naphthylene, glycerine monoallyl ether, trimethylol propane monoallyl ether, glycerine monoglycidyl ether, dimethylol propionic acid methyl ester, dimethylol propionic acid bromobutyl ester, esters of monocarboxymethyl ethers of
30
35

glycerine and trimethylol propane and other additional groups which modify the properties of the block polymer.

5 The invention also includes a method for the production of linear block polymers and it is characterized in that a prepolymer having two isocyanate end groups per molecule is chain extended with an aliphatic or aromatic diamine having a mol ratio of NH₂/NCO of 0.95 - 1.05, preferably 0.98 - 1.02.

10 According to the invention, the prepolymer is suitably produced by providing a diol with two isocyanate end groups per molecule. The prepolymer may be a mixture of prepolymers having different composition.

15 According to the invention, it is suitable that the diol consists of a polyester diol, for example, polydiethylene glycol adipate diol, polycapro-lactone diol or polyethylene glycol adipate diol, or a polyether diol such as 20 polytetramethylene oxide diol, polyethylene oxide diol or a monodiol such as glycerine monoallyl ether, trimethylol propane monoallyl ether, glycerine monoglycidyl ether, dimethylol propionic acid methyl ester, dimethylol propionic acid bromobutyl ester, esters of 25 monocarboxymethyl ethers of glycerine, trimethylol propane, and others and the isocyanate-supplying compound is suitably 4, 4'-diphenyl methane diisocyanate, toluylene diisocyanate, hexamethylene diisocyanate, tetramethylene diisocyanate, naphthylene diisocyanate and others. The diol 30 may also consist of mixtures of diols.

35 According to the invention, it is suitable that the diamine consists of primary diamines, preferably ethylene diamine or 1,3-diaminopropane or hydrolysable diamines, for example, 1,3-propane diol-bis-p-aminobenzoate or ethylene glycol-bis-diamino acetate.

The molecular weight and its distribution may, according to the invention, be controlled by the stoichiometric relationship but primarily by addition of small amounts of monoamine, for example butyl amine or ethanol amine.

5

The method according to the invention also includes that built-in groups in the chain are modified by a reaction with physiologically active substances. Those groups which, according to the invention, are modified are suitably glycerine monoallyl ether, trimethylol propane monoallyl ether, glycerine monoglycidyl ether, dimethylol propionic acid methyl ester, and dimethylol propionic acid bromobutyl ester.

10

15

The linear block polymer according to the invention is suitable as material in implants in humans and animals.

20

When the block polymer is used as an implant this is suitably an implant for ligaments, tendons, skin or cartilage.

25

According to the invention, it is suitable that when the polymer is used as an implant it has the form of fibres or threads which have been knitted or woven.

30

According to the invention, it is suitable that the block polymer, by means of its NH₂ or OH end groups, is used for covalent binding of growth-promoting groups. The OH groups can be obtained by, for example, using ethanol amine as a chain stopper.

DETAILED DESCRIPTION:

Block polymers or block copolymers are defined as copolymers in which participating monomers are present as sequences or blocks of different lengths which are linearly united to each other to molecules having a high molecule

weight ($>10^4$ Dalton). The latter is important for the mechanical properties and necessary for making fibres and films.

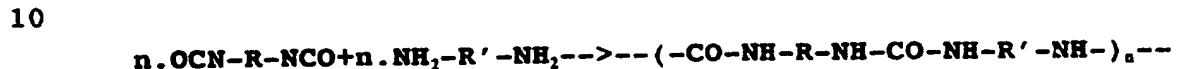
5 An advantage of block polymers is that properties which are characteristic for several homopolymers can be built in in one and the same molecule. In this way, incompatible polymers can be brought to cooperate in a material and apparently non-compatible properties can be combined. Thus,
10 reactive side groups can be introduced. Further, hydrolysable blocks may, for example, be introduced which, after hydrolysis, give fragments of polymers which are sufficiently small to be secreted from the body.

15 A common way to describe block polymers is as follows. The monomer A forms the block A-A-A-A-A..., called polyA or pA and the monomer B forms the block B-B-B-B..., polyB or pB. They are united to -A-A-A-A-B-B-B- or pA-pB in the production process. Typical block polymer types are
20 diblock, triblock and multiblock polymers. In the present invention, the multiblock type is the one mostly used. It is written pA-pB-pA-pB-pA-pB... in which the block types alternate. By partially exchanging the block types, variants can be produced which give further properties to
25 the polymer. The invention relates to production of such variants in which the third component (and possibly a fourth) randomly replaces one of the blocks, for example pB.

30 The invention uses isocyanate chemistry to synthesise the block polymers, which will be of the type polyurethane urea since the polymer chain contains both urethane and urea groups. Both form hydrogen bonds between the molecules, which gives the cohesive forces which are needed to keep
35 the molecules together in a material. Especially strong intermolecular forces are obtained by the urea groups

especially when several groups have the possibility to cooperate. For this reason, the cohesive forces grow strongly when the amount of urea blocks increases.

5 The polyurea blocks will henceforth be denoted by pA and the others by pB, pC, etc. They are usually formed at the chain extension when the isocyanate group-terminated prepolymers are coupled to diamines according to the formula



in which OCN-R-NCO is a urethane diisocyanate formed of a diol and a diisocyanate according to the formula

15 $HO-R''-OH + 2 OCN-R'''-NCO \rightarrow OCN-R'''-NH-CO-O-R''-O-CO-NH-R'''-NCO$ in which R is pB, pC, etc. blocks as above. In the reaction the stoichiometry is very important. Thus, n must have so great a value that it corresponds to molecular weights of at least 10^4 , preferably 10^5 or more, if satisfactory mechanical properties are to be obtained. To reach such high values the molar ratios of $-NH_2/-NCO = 0.95 - 1.05$ are used. The excess of $-NH_2$ gives end groups of a primary amine character which can be used to covalently attach biologically active groups to the polymer molecules.

20 If ethanol amine is used as a chain stopper, OH end groups are obtained which also can be used for coupling of active agents, for example growth factors to the polymer. Excess of isocyanate groups gives end groups which can react further according to known isocyanate reactions.

25

30 If better mechanical properties are desired by means of more and/or longer urea blocks, this can be obtained in, for instance, the following two ways:

35 1. During the chain extension reaction further diisocyanate and a corresponding amount of diamine are added. Care must

be taken when increasing the average length of the urea blocks since formation of unmeltable gel can be obtained even on a moderate increase of the length.

5 2. An isocyanate group terminated prepolymer containing urea groups is added during the chain extension reaction. The prepolymer must be dissolved in the reaction mixture when the reaction of the chain extension is started.

10 As a chain extender, primary diamines are preferably used, which may be aliphatic or aromatic. Primary aliphatic diamines give very high reaction velocity, which can cause inhomogeneous reactions and hence an inhomogeneous product. The reaction velocity can be modified by using aromatic amines the structure of which is very significant for the reactivity or by adding some agent which cooperates with the amine and/or isocyanate groups such as acetone, oximes, or the like. Considerable possibilities to control the activity are consequently present.

15 20 The chain extension may also occur in solvents which dissolve the starting products but not the polymer. The product precipitates, for example, as a powder and it can then be obtained by filtering.

25 30 35 The polyurea blocks pA are often called "hard" since they are responsible for the cohesion of the materials, which is a function of the content and the length thereof. Correspondingly, the pB are often called "soft" blocks since they give the materials the stretchability and elasticity. In known materials produced on a large scale they consist of polytetramethylene oxide diol. Other examples are polyethylene oxide diol, polycaprolactone diol, polyethylene glycol adipate diol, etc. All of them have hydroxyl end groups and are transformed to prepolymers by reaction with diisocyanates according to the formula:



In the formula two mol diisocyanate per mol diol have been stated. This gives the shortest possible prepolymer. If longer prepolymers are wanted, less than two mol diisocyanate per mol diol is used according to known relations from polymer chemistry. At the reaction urethane groups are formed. It can be carried out at an elevated temperature ($60-80^\circ\text{C}$) or at lower temperatures in the presence of a catalyst. Too high temperatures ($>90^\circ\text{C}$) should be avoided to minimise non-desired side reactions, for example, di- or trimerising of the isocyanate.

The isocyanates used in the invention must be bifunctional so that the formed polymers are linear and can form fibres and films. Preferably, the content of bifunctional molecules should be greater than 99%. If the impurities consist of agents that do not take part in the reaction, then a somewhat lower content of isocyanate can be tolerated. If monoisocyanates are present they will bring about a termination of the molecules. If isocyanates having three or more isocyanate groups are present, branched molecules or cross-bound polymers are formed which cannot be spun to fibres or form films. Among useable isocyanates, toluylene diisocyanate (TDI), diphenylmethane-4,4'-diisocyanate (MDI), hexamethylene diisocyanate (HDI), tetramethylene diisocyanate, naphthylene diisocyanate, and others may be mentioned.

In a corresponding way to that described above, prepolymers for other functional blocks (pC, pD, etc.) can be produced. In principle, every diol which does not contain other groups than hydroxyl groups which react with isocyanate can be used. Examples thereof are glycerine monoallyl ether, trimethylol propane monoallyl ether, glycerine monoglycidyl ether, dimethylol propionic acid methyl ester, dimethylol

propionic acid bromobutyl ester, esters of monocarboxymethyl ethers of glycerine, trimethylol propane and many others. These either have, or they can be converted by known methods to, epoxy groups which in their turn after the chain extension can be reacted in a number of ways to facilitate binding to biologically active groups such as growth-promoting peptides.

The chain extension reaction is suitably carried out in a solution to decrease the speed of reaction, viscosity and tendency of gel formation. Dimethyl formamide, dimethylacetamide, dimethylsulphoxide or some similar polar solvent may be used as solvents. The solution obtained can be used as a dope for fibre spinning directly or after modification.

Alternatively, as mentioned above, the chain extension may be carried out in an agent which dissolves the starting products but in which the polymer is insoluble. In that case the product is dissolved in a solvent before spinning, which is performed in the same way as above.

The spinning can be done either as dry spinning or as wet spinning according to known methods. The latter method includes that the dope is inserted via the spinning nozzle into water. In connection with the coagulation, the fibre bunch may be stretched to the desired stretching degree, whereupon the thread is wound up while being simultaneously twisted.

In an analogous way, film can be produced by moulding on rollers, coagulating, stretching and winding up. The stretched film can thereafter be cut into fibre-like strips.

EXAMPLE 1

Polydiethylene glycol adipate diol with a molecular weight of 560 was dried in vacuum for 16 hours. In a three-necked flask with thermometer and stirrer 90.78 g of crystalline 5 4,4'-diphenyl methane diisocyanate (MDI) was melted, whereupon 99.86 g polydiethylene glycol adipate diol having a molecular weight of 560 was added dropwise during heating. The reaction temperature was maintained by cooling between 80 and 90°C. The reaction was complete after four 10 hours. The content of isocyanate was determined titrimetrically and was 1.22.

The prepolymer obtained (22.81 g) was dissolved in dimethyl formamide to a concentration of 20%. It was chain extended 15 using a slight excess of ethylene diamine (1.05 g) at room temperature under most possible effective stirring. The reaction was complete a few minutes after the addition was completed.

20 Film was produced by spreading out the solution on a glass plate and evaporating the solvent in a desiccator cabinet. The film obtained was flexible and mechanically strong even in a humid atmosphere.

25 The solution was wet-spun by extrusion through a spinning nozzle having 50 orifices with a diameter of 80 µm in a water bath. The fibre bunch obtained (the thread) was stretched 5 times in a subsequent water bath and wound up on a bobbin. After rinsing in water for two days and 30 drying, the strength was measured in a tensioning measuring apparatus to 1.6 N and the break elongation was 70%. Bands were woven from the fibres and surgically inserted into rabbit knees.

EXAMPLE 2

102.2 g of a polycaprolactone diol having a molecular weight of 2000 was added dropwise to 17.19 g hexamethylene diisocyanate at a temperature of 80-90°C during three
5 hours. 42.1 g of the product, which had an isocyanate number of 0.78, was dissolved to a 25% solution in dimethyl formamide. The solution was cooled to 0°C and reacted under vigorous stirring with 0.96 g ethylene diamine and 0.039 g ethanol amine. The reaction was practically instantaneous.

10 After dilution with dimethyl formamide to a concentration of 15% and addition of 12 g LiCl, a clear solution was obtained which was wet-spun in water through a nozzle having 50 orifices with a diameter of 80 µm, stretched six
15 times and wound up on a bobbin. After rinsing in water, the thread had a break strength of 1.18 N and a break elongation of 80 %.

EXAMPLE 3

20 118 g dry polycaprolactone having a molecular weight of 530 was added dropwise to 11.32 g diphenyl methane diisocyanate (MDI) while the temperature was maintained at 70-80°C during 2 hours. From the prepolymer formed (isocyanate number 1.98) 16.13 g was dissolved in dimethylsulphoxide
25 (DMSO) to a 15% solution and 0.95 g ethylene diamine and 0.04 g ethanol amine dissolved in DMSO was added at 20°C. The solution, which rapidly became highly viscose, was stirred for one hour, whereupon it was wet-spun in the same way as in Example 1. The thread obtained had a break strength of 1.1 N and the break elongation was 22%. The
30 thread had the text number 7.

EXAMPLE 4

35 98.78 g dry polycaprolactone with a molecular weight of 1250 was added dropwise to 39.51 g MDI during 3 hours at a maintained temperature of 70-80°C. From the prepolymer,

which had the isocyanate number 1.2, 30.48 g was dissolved in acetone and 1.13 g ethylene diamine was added under vigorous stirring at 20°C. A white pulverulent product was formed which could be dissolved in DMF + LiCl and wet-spun to a thread. The break tension was 2.18 N and the break elongation 175%.

EXAMPLE 5

A prepolymer was produced from 47.58 g poly(1,4-butane diol adipate) with a molecular weight of 600 and 90.2 g MDI by adding the dry polyester dropwise into the melted isocyanate for 2 hours at a maintained temperature of 70-80°C. The isocyanate number for the finished prepolymer was 1.61.

29.78 g was taken from the prepolymer and dissolved to a 30% solution in dimethylsulphoxide (DMSO). 7.72 g 1,3-propane diol-bis-p-aminobenzoate was added and chain extension was carried out at 100°C during 22 hours while stirring. A clear solution was obtained which could be spun to fibres according to the method given in Example 1. The thread was stretched 4 times. The break tension was 0.8 N and the break elongation 200%.

The polymers according to the invention can be fragmented in a biological environment and they can be bound to growth-promoting groups. They are film and fibre forming and they have mechanical properties sufficient for the production of woven or twisted bands useful as ligament prostheses.

As stated above, the polymers according to the invention can be used both as temporary and permanent implants. If the implant is to be temporary, it is connected in a suitable surgical way to the damaged body part, for example the ligament, whereupon the damaged body part can grow and

13

heal with the protection and assistance of the implant. After the healing is complete, this can be removed or it can be fragmented during the healing and be secreted from the body.

5

The invention is not limited to the above-stated embodiments but can be varied in different ways within the scope of the claims.

10

1997-04-09

14

5 CLAIMS

1. Linear block polymer having a molecular weight of at least 10^4 Dalton, preferably at least 10^5 Dalton, comprising urea and urethane groups and including primary NH₂ and/or OH end groups.

2. Linear block polymer according to claim 1, characterized in that the urea groups are equal with or greater in number than the urethane groups.

15 3. Linear block polymer according to any of claims 1 or 2, characterized in that in the chain it also contains groups derived from polytetramethylene oxide, polyethylene oxide, polycaprolactone, polyethylene glycol adipate, toluylene, diphenyl methane, hexamethylene, tetramethylene, naphthylene, glycerine monoallyl ether, trimethylol propane monoallyl ether, glycerine monoglycidyl ether, dimethylol propionic acid methyl ester, dimethylol propionic acid bromobutyl ester, esters of monocarboxymethyl ethers of glycerine and trimethylol propane and other additional groups which modify the properties of the block polymer.

30 4. Method for the production of linear block polymers according to any of claims 1-3, characterized in that a prepolymer having two isocyanate end groups per molecule is chain extended with an aliphatic or an aromatic diamine having a mol ratio NH₂/NCO of 0.95 - 1.05, preferably 0.98 - 1.02.

35 5. Method according to claim 4, characterized in that the prepolymer is produced by providing a diol with two isocyanate groups per molecule.

6. Method according to claim 5,
characterized in that the diol is a
polyester diol, for example, polycapro-lactone diol
5 polydiethylene glycol adipate diol or polytetramethylene
oxide diol, polyethylene oxide diol, polyethylene glycol
adipate diol, glycerine monoallyl ether, trimethylol
propane monoallyl ether, glycerine monoglycidyl ether,
dimethylol propionic acid methyl ester, dimethylol
10 propionic acid bromobutyl ester, esters of
monocarboxymethyl ethers of glycerine and trimethylol
propane, and the isocyanate-supplying compound of 4,4'-
diphenyl methane diisocyanate, toluylene diisocyanate,
hexamethylene diisocyanate, tetramethylene diisocyanate,
and naphthylene diisocyanate.

15

7. Method according to any of claims 4-6,
characterized in that the diamine consists
of primary diamines, preferably ethylene diamine or
hydrolysable diamines, for example DMAB or ethylene glycol
20 bis glycine ester diamine.

8. Method according to any of claims 1-7,
characterized in that the molecular weight
and its distribution are controlled by stoichiometry or by
25 addition of small amounts of monoamine, for example butyl
amine or ethanol amine.

9. Method according to any of claims 1-8,
characterized in that built-in groups in the
30 chain are modified by reaction with physiologically active
substances.

10. Method according to claim 9,
characterized in that the groups consist of
35 glycerine monoallyl ether, trimethylol propane monoallyl

ether, glycerine monoallyl ether, dimethylol propionic acid methyl ester, dimethylol propionic acid bromobutyl ester.

11. Use of the linear block polymer according to any of
5 claims 1-3 as material in implants in humans and animals.

12. Use according to claim 11,
characterized in that the block polymer is
part of or wholly an implant for ligaments, tendons, skin
10 or cartilage.

13. Use according to any of claims 11 or 12,
characterized in that the block polymer is
present in the form of fibres or threads and is knitted or
15 woven.

14. Use according to any of claims 11-13,
characterized in that the NH₂ or OH end
groups of the block polymer are used for covalent binding of
20 growth-promoting groups.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01530

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C08G 18/10, C08G 18/32, A61L 27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C08G, A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0461375 A1 (CORVITA CORPORATION), 18 December 1991 (18.12.91), claims 1,20 --	1-14
X	WO 8905319 A1 (TYNDALE PLAINS-HUNTER, LTD.), 15 June 1989 (15.06.89), abstract --	1-14
X	WO 9200338 A1 (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION), 9 January 1992 (09.01.92), claims 1,12 --	1-14
X	WO 9204390 A1 (POLYMEDICA INDUSTRIES, INC.), 19 March 1992 (19.03.92), claim 1, abstract --	1-14

 Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

24 March 1997

Date of mailing of the international search report

29 -03- 1997

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Jack Hedlund
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

04/03/97

International application No.	
PCT/SE 96/01530	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0461375 A1	18/12/91	CA 2038605 A DE 9117117 U DE 69112911 D,T ES 2077104 T JP 4226119 A US 5133742 A US 5229431 A		16/12/91 01/02/96 02/05/96 16/11/95 14/08/92 28/07/92 20/07/93
WO 8905319 A1	15/06/89	AU 2800489 A CA 1338678 A EP 0400015 A JP 3501496 T US 5120816 A US 5334691 A		05/07/89 22/10/96 05/12/90 04/04/91 09/06/92 02/08/94
WO 9200338 A1	09/01/92	AU 657267 B AU 8006591 A EP 0536223 A US 5393858 A		09/03/95 23/01/92 14/04/93 28/02/95
WO 9204390 A1	19/03/92	AU 664158 B AU 8645491 A CA 2091564 A EP 0548256 A US 5254662 A		09/11/95 30/03/92 13/03/92 30/06/93 19/10/93

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)